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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/009,477	12/11/2001	Masahiro Imoto	1830/50521	4095

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EXAMINER
RAO, DEEPAK R

ART UNIT	PAPER NUMBER
1624	6

DATE MAILED: 09/25/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
10/009,477	Imoto et al.
Examiner	**Art Unit**
Deepak Rao	1624

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Dec 11, 2001* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-34* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-34* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☒ None of:

1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *2 & 5*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims 1-34 are pending in this application.

Election/Restrictions

Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

Group I, claim(s) 1-34 (in part), drawn to compounds of formula (I) wherein X is -$C(R^1,R^2)$-$C(R^3,R^4)$- or -$C(R^5)$=$C(R^6)$- (i.e., imidazoline compounds), corresponding composition and method of use.

Group II, claim(s) 1-34 (in part), drawn to compounds of formula (I) wherein X is -$C(R^7,R^8)$-$C(R^9,R^{10})$-$C(R^{11},R^{12})$- (i.e., tetrahydropyrimidine compounds), corresponding composition and method of use.

Group III, claim(s) 1-34 (in part), drawn to compounds of formula (I) wherein X is -$C(R^{13},R^{14})$-$C(R^{15},R^{16})$-NH- (i.e., 1,2,4-triazine compounds), corresponding composition and method of use.

The inventions listed as Groups I-III do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The compounds of Groups I-III are drawn to structurally dissimilar compounds. They are made independently and used independently. They would be expected to raise different issues of patentability if for example, imidazoline compounds of Group I were anticipated, the anticipatory reference would not necessarily render obvious the compounds of Groups II-III or vice-versa. Further, there is no common technical feature in inventions of Groups I-III and they do not share the same technical features as required by PCT Rules 13.2 and 13.3.

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1. Applicant is required to elect a single disclosed species falling within the elected group, even though this requirement is traversed. The reply must also identify the claims readable on the elected species, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered non-responsive unless accompanied by an election.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the

examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

During a telephone conversation with Mr. Herbert Cantor on September 17, 2002 a provisional election was made with traverse to prosecute the invention of Group II, claims 1-34 (in part) and the species of Compound No. 2 in Table 1. Affirmation of this election must be made by applicant in replying to this Office action.

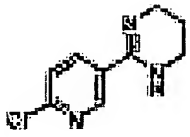
Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Applicant's election of the species of Compound No. 2 (page 29, Table 1) is acknowledged. The species represents a compound of formula (I) wherein:

X is $-CH_2-CH_2-CH_2-$;

A^1 is H; and

A^2 is 6-chloro-pyrid-3-yl.



The guidelines in MPEP § 803.02 provide that upon examination if prior art is found for the elected species, the examination will be limited to the elected species.

Content of MPEP § 803.02 is provided here for convenience:

> As an example, in the case of an application with a Markush-type claim drawn to the compound C-R, wherein R is a radical selected from the group consisting of A, B, C, D and E, the examiner may require a provisional election of a single species, CA, CB, CC, CD or CE. The Markush-type claim would then be examined fully with respect to the elected species and any species considered to be clearly unpatentable over the elected species. If on examination the elected species is found to be anticipated or rendered obvious by prior art, the Markush-type claim and claims to the elected species shall be rejected, and claims to the non-elected species would be held withdrawn from further consideration. As in the prevailing practice, **a second action on the merits on the elected claims would be final.**
> On the other hand, should no prior art be found that anticipates or renders obvious the elected species, the search of the Markush-type claim will be extended. If prior art is then found that anticipates or renders obvious the Markush-type claim with respect to a nonelected species, the Markush-type claim shall be rejected and claims to the nonelected species held withdrawn from further consideration. **The prior art search, however, will not be extended unnecessarily to cover all nonelected species.** Should applicant, in response to this rejection of the Markush-type claim, overcome the rejection, as by amending the Markush-type claim to exclude the species anticipated or rendered obvious by the prior art, the amended Markush-type claim will be reexamined. The prior art search will be extended to the extent necessary to determine patentability of the Markush-type claim. In the event prior art is found during the reexamination that anticipates or renders obvious the amended Markush-type claim, the claim will be rejected and the action made final. Amendments submitted after the final rejection further restricting the scope of the claim may be denied entry.

The elected species identically was not found in the prior art search and the search was expanded to the subgenus of formula (I) wherein X and A^1 are as indicated above and A^2 is optionally substituted pyridyl and art was found. As per the guidelines of MPEP § 803.02, the Markush-type claims were examined to the extent of the searched subgenus. The non elected species and the generic subject matter (i.e., all other definitions of X, A^1 and A^2) drawn to the non elected species from claims 1-34 is withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to non-elected inventions.

Claim Objections

Claims 22-25 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim can not depend from any other multiple dependent claim. See MPEP § 608.01(n). Accordingly, the claims have not been further treated on the merits. In the instant case, claim 22 multiply depends from claim 3 or 4 of which claim 3 is a multiple dependent claim.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5-21 and 26-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of depression and anxiety, does not reasonably provide enablement for preventing or treating of all types of cerebral circulation diseases, neurodegenerative diseases, etc. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the

art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

The scope of the method claims is not adequately enabled solely based on the activity related to α4β2 nicotinic acetylcholine receptor activity provided in the specification. The claim language includes diseases that are known and those that are yet to be discovered, for which there is no enablement. First, the instant claims cover 'diseases' that are known to exist and those that may be discovered in the future, for which there is no enablement provided. The use disclosed in the specification is as pharmaceutical therapeutic agents having affinity for α4β2 nicotinic acetylcholine receptors, useful to treat a laundry list of diseases, which include neurodegenerative diseases, inflammatory intestinal diseases, etc. Test assays and procedures are provided in the specification at pages 43-52, wherein the *Ki* data for some of the compounds of the invention is provided in Table 1, however, there is nothing in the disclosure regarding how this data correlates to the treatment of the diverse disorders of the instant claims. The disorders encompassed by the instant claims include neurodegenerative diseases, etc., some of which have been proven to be extremely difficult to treat. A state of the art reference, Levin et al. (AD in IDS) expresses that there are many unanswered questions regarding 'the relationship of nicotinic involvement in cognitive function to nicotinic involvement in other types of function', see page 226, col. 2. Also, Holladay et al. (AU in IDS) remarks that "The possible contributions of presently unknown subunits and the existence of more than one nAChR subtype in the same tissue continues to present challenges..." thereby providing the complexities involved in

pharmacological responses of nAChRs. Further, there is no reasonable basis for assuming that the myriad of compounds embraced by the claims will all share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent and there is no basis in the prior art for assuming the same. Note *In re Surrey*, 151 USPQ 724 regarding sufficiency of disclosure for a Markush group.

Further, the list of the central nervous system disorders includes neurodegenerative diseases (see claim 31) which covers diverse disorders such as Alzheimer's disease, dementia, hereditary cerebellar ataxias, paraplegias, syringomyelia, phakomatoses, and much more. In fact, Layzer, Cecil Textbook of Medicine (article enclosed), states that "some degenerative diseases are difficult to classify because they involve multiple anatomic locations" (see page 2050). For example, Alzheimer's disease has traditionally been very difficult or impossible to prevent or even to treat effectively with chemotherapeutic agents. See e.g., the Cecil Textbook of Medicine, 20th edition (1996), Vol. 2, wherein it is stated that "[t]here is no cure for Alzheimer's disease, and no drug tried so far can alter the progress of the disease." (pg. 1994).

The instant claims are drawn to 'A method of **preventing** or treating....' several diseases, and therefore, the instant claim language embraces disorders not only for the treatment, but for "prevention" which is not remotely enabled. Based on the affinity for $\alpha 4\beta 2$ nicotinic acetylcholine receptors, the instant compounds are disclosed to be useful in the "prevention" of neurodegenerative diseases, cerebral circulation diseases, etc., for which applicants provide no competent evidence. "To prevent" actually means *to anticipate* or *counter in advance, to keep*

from happening etc. (as per Websters II Dictionary) and therefore it is not understood how one skilled in the art can reasonably establish the basis and the type of subject to which the instant compounds can be administered in order to have the 'preventive' effect. It is inconceivable from the test data of a small number of representative compounds can be correlated to the 'method of **preventing** or treating' of the various claimed disorders, such that the claimed compounds can not only treat but also "prevent" a myriad of diseases associated with the stated activity. Further, there is no evidence on record which demonstrates that the screening test relied upon is recognized in the art as being reasonably predictive of success in any of the contemplated areas of 'prevention'. Such a reasonable correlation is necessary to demonstrate such utilities. See *Ex parte Stevens*, 16 USPQ 2d 1379 (BPAI 1990); *Ex parte Busse et al.*, 1 USPQ 2d 1908 (BPAI 1986) (the evidence must be accepted as "showing" such utility, and not "warranting further study"). Furthermore, there is no evidence of record which would enable the skilled artisan in the identification of the people who have the potential of becoming afflicted with the disorders encompassed by the instant claims.

Part of the difficulty of developing drugs effective for **preventing** of neurodegenerative diseases, etc. lies in the lack of understanding as to why people come down with these disorders and the numerous causes of these disorders. See Maelicke et al. (AT in IDS) stated in their reference: "In spite of the existence of several theories regarding the pathogenesis of AD, the molecular causes of the condition are still unknown", see page 54. Lin et al. (AM in IDS) listed several **obstacles** in drug development and expressed regarding the therapeutic potential of

nAChRs, "Although several of these compounds have entered clinical evaluation, none has convincingly demonstrated clinical efficacy for its targeted disease state", see page 1009. Also, Nordberg et a. (AI in IDS) concluded that "Further knowledge about the functional activity of the cholinergic receptors and their role in regulation of transmittor release and signal transduction will be important for the development of putative therapeutic agents in dementia disorders", see page 110. Sandborn et al. (AH in IDS) also expressed 'the need for additional studies to determine the efficacy of the nicotinic therapy for treatment of intestinal inflammation', see page 371. Kihara et al. (AG in IDS) also indicate that 'nicotinic receptors show additional complexities, with ligand binding' and conclude with 'speculative' remarks that they "may have effects that counter the progress of AD".

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the use of the invention. In view of the breadth of the claim, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-21 and 26-34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reasons apply:

1. Claim contains a plural in the preamble, i.e., "Cyclic amidine **compounds**" which appears to be drawn to a mixture of compounds. Replacing the phrase with --A compound -- is suggested. Also, in the last line the recitation of "**salts**" be replaced by -- salt --. Claim 34 also contains "**Compounds**" in line 1 which should be replaced with -- The compound --.

2. In claim 2, last line on page 56, there is a period at the end of the line and the claim continues on the following page. It is not clear if the first line on page 57 is intended to be part of claim 2 or not. Deletion of the period at the end of the last line on page 56 is suggested.

Claims not particularly addressed above are included because they do not further resolve the above issues.

Claim Rejections - 35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

1. Claims 1, 3-9 and 14-18 are rejected under 35 U.S.C. 102(a) as being anticipated by Maguire et al., WO 01/10842 (published February 15, 2001). The instantly claimed compounds read on the reference disclosed compounds see compounds DF (page 108), IE (page 121), etc.

Applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

2. Claims 1, 3-9 and 14-18 are rejected under 35 U.S.C. 102(b) as being anticipated by Kolaczkowska et al., Chem. Abstract 112:35878 (1990). The instantly claimed compounds of formula (I) read on reference disclosed compound: 1,4,5,6-tetrahydro-2-(2-pyridinyl)-pyrimidine (RN: 124345-86-4). The intended use in the composition claims is not given patentable weight.

3. Claims 1, 3-9 and 14-18 are rejected under 35 U.S.C. 102(b) as being anticipated by Frei et al., GB 2082577. The instantly claimed compounds read on the reference disclosed compound, see formula (II) and the compound disclosed in Example 54: 4-amino-3-(1,4,5,6-tetrahydro-2-pyrimidinyl)-pyridine (page 15, line 41).

4. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Kwok, Chem. Abstract 89:179949. The instantly claimed compounds read on reference compounds, see the reference disclosed compounds in the enclosed copy of the CAPLUS computer search report.

5. Claims 1, 3-21 and 26-34 are rejected under 35 U.S.C. 102(b) as being anticipated by Walker et al., Chem. Abstract 87:111268. The instantly claimed compounds read on the reference disclosed compound, see RN 35059-05-3 in CAPLUS report. The reference discloses that the compound has nicotinic agonistic activity.

6. Claims 1, 3-21 and 26-34 are rejected under 35 U.S.C. 102(b) as being anticipated by Upshall, Chem. Abstract 77:70055. The instantly claimed compounds read on the reference disclosed compound, see RN 35059-05-3; RN 38108-28-0, etc. in CAPLUS report. The reference discloses that the compound has nicotinic activity.

Duplicate Claims

Applicant is advised that should claims 3-4 be found allowable, claims 5-9 and 14-18 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). In the instant case, claims 5-9 and 14-18 recite an intended use of the composition or medicament without setting forth any positive steps or limitations and accordingly, they are substantial duplicates of claims 3 and 4 respectively.

Receipt is acknowledged of the Information Disclosure Statements filed on December 11, 2001 and May 29, 2002 and a copies are enclosed herewith.

Priority

The application claims benefit to international application No. PCT/JP01/03378 filed on April 20, 2001. Applications that are filed on or after November 29, 2000, and that claim benefit to an earlier-filed international application must include in the first sentence of the specification **an indication of whether the international application was published in English** under PCT Article 21(2) (regardless of whether the benefit for such application is claimed in an application data sheet). See 37 CFR 1.78(a)(2). The indication, as required by 37 CFR 1.78(a)(2), is missing. Applicant must supply the missing indication as an amendment to the specification in the reply to this Office action.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (703) 305-1879. The examiner can normally be reached on Tuesday-Friday from 6:30am to 5:00pm. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4556. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

Deepak Rao
Primary Examiner
Art Unit 1624

September 25, 2002